

# State of the Science on the Carcinogenicity of Gasoline with Particular Reference to Cohort Mortality Study Results

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As a result of the content of benzene in various streams of refinery products, including gasoline, it is not surprising that over the years studies and case reports have linked gasoline exposure to lymphopoietic cancers (LPC), particularly leukemia and multiple myeloma (MM). Of three recently conducted studies of gasoline-exposed workers, one shows strong associations with leukemia and MM, a second suggests some association with leukemia and did not analyze data for MM, and the third study is not possible to evaluate because of a major problem with study design. Other diseases of particular interest in relation to gasoline exposure are kidney cancer, malignant melanoma, and heart disease. One study suggests an association with kidney cancer, but the second study did not. There appears to be no association between employment in refineries or gasoline exposure and heart disease. However, evaluation of risk of kidney cancer and heart disease is somewhat difficult because investigators did not control for cigarette smoking, even though it is related to these diseases. This is of particular concern when studying gasoline-exposed workers, who because of the explosive nature of gasoline probably smoke less than the general population used for comparison of mortality. Some studies of refinery workers and gasoline-exposed workers in particular show an excess risk of death from malignant melanoma. Whether this latter association is the result of benzene/gasoline exposure, sunlight exposure, or a combination of the two cannot be determined with the data currently available. The National Toxicology Program benzene cancer bioassay and the Dow Chemical Company epidemiologic study argue in favor of a benzene etiology; the fact that the workers spend a great amount of time outdoors argues in favor of a sunlight etiology. Finally, the American Petroleum Institute is challenged to apply cancer and blood disease warning labels and filling instructions to gasoline pumps and containers to prevent the misuse of gasoline and the subsequent development of MM, leukemia, and other blood diseases that can be caused by exposure to benzene and gasoline.

## Introduction

Benzene is a contaminant of gasoline. Its volume percent in gasoline in the United States has averaged between 1.5 and 2.0% over the past decade (Motor Vehicle Manufacturers Association Survey results, personnel communication), but concentrations slightly over 5% have been measured in gasoline at the pump (1). Thus, it is not surprising that the literature contains case reports and epidemiologic studies of blood diseases associated with gasoline exposure that parallel the sequence of case reports and epidemiologic findings of blood diseases associated with benzene exposure; however, the information on gasoline and blood diseases lags the benzene literature by a few decades. For example, case reports of aplastic anemia (2,3), hemolytic anemia (3), myelofibrosis (3,4), neutropenia (3,5), thrombocytopenia (3,5), and myeloid metaplasia (4) associated with gasoline exposure have

been followed by case reports of leukemia (4,6) associated with exposure to gasoline. These same blood diseases have all been associated with occupational exposure to benzene. Epidemiologic analyses have also demonstrated elevated risks of leukemia and other blood diseases among workers exposed to gasoline (6-9).

In the early 1980s, a study by Thomas et al. (10) provided the stimulus for a large number of studies that subsequently demonstrated increased risks of lymphopoietic cancers (LPC) among refinery workers. The demonstration of these excess risks again was not surprising, as there is potential for benzene exposure among refinery populations.

Because of the multiple site carcinogenicity of benzene as demonstrated in experimental animals (11), concern has been expressed that benzene and products containing benzene may cause more than lymphopoietic cancer in humans. This concern became heightened as a result of the toxicologic study demonstrating kidney cancer in male rats exposed to gasoline vapor and findings in some of the earlier epidemiologic studies of refinery workers showing an elevation of site-specific cancers not related to the lymphopoietic system, though the latter findings were

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inconsistent. Because cardiovascular disease is the major cause of death in industrialized countries, analyses for this cause of death were also reviewed. Thus, the more recent studies of gasoline-exposed workers have focused particularly on kidney cancer, multiple myeloma (MM) and other lymphatic cancer, leukemia, malignant melanoma, and heart disease.

## Kidney Cancer

Of the studies presented at the gasoline symposium, only the Schnatter et al. study (12) provides some evidence of an association between gasoline exposure and kidney cancer. The data of this study were internally consistent in that every measure of increasing exposure showed an increasing risk of death from kidney cancer. For example, the standardized mortality ratio (SMR) for kidney cancer was 135 for the total cohort and 158 for those employees characterized as experiencing "total hydrocarbon" exposure (12). When the authors analyzed their data by exposure frequency, those workers who would have had greater exposure, e.g., categorized as "nonexposed," less than daily exposed, or daily exposed, the SMRs for kidney cancer were 91, 99, and 208, respectively. For tank truck drivers, who were characterized as experiencing the highest exposures, the SMR for kidney cancer was 210. This analysis, however, was based on a small number of observations. When data for kidney cancer were analyzed using a Poisson regression model, a relative risk of about 4.0 was observed for those exposed daily as compared to those exposed less than daily.

The study presented by Rushton (13), which appears to be in the early stages of analysis, shows an SMR for kidney cancer of 101 in refinery workers and an SMR of 127 for distribution workers in comparison to expected mortality based on the general population. The latter SMR was not significantly elevated. Cigarette smoking, however, is related to kidney cancer, and if these workers smoked less than the general population because of the danger of gasoline explosion, use of the general population as a comparison group may overestimate expected mortality from kidney cancer and, hence, underestimate the relative risk of kidney cancer associated with gasoline exposure. Thus, adjustment for cigarette smoking in the Rushton study (13), as well as in all studies of gasoline-exposed workers, needs to be considered in the analyses. In the absence of this adjustment, it is difficult to evaluate the findings with regard to kidney cancer.

The Wong and Harris study (14) appears to have been well conducted, and it has the potential to provide a great deal of information in the future. Currently, the overall SMR of 52 for the land-based workers suggests the general population used in the study is not an appropriate comparison population. Thus, it is difficult to make any meaningful comments about the study results. The same could be said for the marine cohort. No further comments will be made about the Wong and Harris study because of the use of an inappropriate comparison population.

## Conclusion

As the data now stand, one study demonstrates an association between total hydrocarbon exposure from gasoline and kidney cancer in humans (12), and the results were internally consistent. Other studies do not show such an association. Lack of adjustment for cigarette smoking in all of the studies, however, may have resulted in an underestimate of the risk or in an inability to detect an elevated risk.

## Multiple Myeloma

In the Schnatter et al. study (12), multiple myeloma (MM) showed an increase in risk by every measure of increasing exposure. The overall SMR in the study was 183, but those who were characterized as occupationally exposed to hydrocarbons had an SMR of 199. When data were presented for those nonexposed, exposed less than daily, or exposed daily, the SMRs for MM were 154, 167, and 228, respectively. Tank truck drivers (another group with high potential exposure) had an SMR of 201, but this was based on only one observed death. The Rushton study (13) did not provide analyses for MM.

Difficulties in identifying associations with MM arise from the rarity of the disease ( $2-3 \times 10^5$ ) and the fact that investigators usually have not separated MM from other forms of lymphoma when presenting cohort study results. Thus, it is not possible to know the contribution of MM to the excesses of death reported for a broad category of death from lymphoma. Nevertheless, in a few studies of petroleum refinery workers where data were presented separately for MM, elevated risks have been observed (10,15-17). Residence in petroleum manufacturing counties also has been associated with a slightly elevated risk of MM (18). The most recent update of the National Institute of Occupational Safety and Health study of benzene-exposed workers demonstrates a statistically significant excess of death from MM (19). Three of the four workers who died from MM in the Rinsky et al. study (19) had low cumulative exposure to benzene and all had a latency of more than 20 years since initial exposure to benzene.

There is a biologically plausible basis for benzene/gasoline to cause MM (15,20). Multiple myeloma is a tumor of plasma cells within the bone marrow, which are derived from lymphocytes. The bone marrow is a target organ for benzene, which causes cytopenia, aplastic anemia, chromosomal damage to lymphocytes (21,22) and leukemia, including chronic lymphocytic leukemia (23). Thus, the target organ and cells of B-lymphocyte lineage are known to be affected by benzene.

## Conclusion

In light of prior evidence of an association between benzene and MM, the increased risk of MM observed in the Schnatter et al. study (12) of gasoline-exposed workers is meaningful. A few other studies that presented data separately for MM also suggest elevated risks for MM in relation to employment in refineries (10,15-17). In my

opinion, the elevated risk of MM observed among gasoline-exposed workers and refinery workers in general is consistent with a benzene etiology. As mentioned above, there is a biologically plausible basis for this association.

## Leukemia

In the Schnatter et al. study (12), leukemia is significantly elevated in the group of truck drivers (highest exposure; SMR = 335). The lack of a dose response for leukemia by exposure frequency in this study is probably a reflection of the small number of workers in the study.

In the recent Rushton study (13), leukemia was slightly lower than expected for refinery workers and slightly higher than expected for distribution workers. Elevations in leukemia risk were associated with various jobs. Perhaps case-control studies could shed some light on these observations. In the earlier reports of these refinery workers by Rushton and Alderson (24), an elevated risk of leukemia was not observed among the entire cohort; however, when a case-control study was conducted, a significantly elevated risk of leukemia was observed among the workers categorized as having medium or high exposure to benzene in comparison to those with low benzene exposure when length of service was taken into account (25).

A number of studies of refinery workers have demonstrated an elevated risk of leukemia (10,15-17,26-29), though the cohort members in these studies were not confined to those who only had exposure to gasoline. Nevertheless, the only ubiquitous leukemogen known to exist in refineries is benzene, and it seems reasonable to conclude that benzene exposures from various sources, including gasoline, is the most likely explanation for this excess risk. In case-control studies of leukemia among refinery workers, significant associations were observed between high- and medium-level exposure to benzene and leukemia (25) and between cumulative benzene exposure and leukemia (17).

## Conclusion

The elevated risk of leukemia observed among gasoline-exposed workers is probably related to the benzene content of gasoline. The elevated risks of LPC in refinery workers in general may be related to benzene because it is the only ubiquitous agent found in refineries that is related to these diseases.

## Malignant Melanoma

The study of Australian refinery workers (17) demonstrates a significantly elevated standardized incidence ratio for malignant melanoma. The Schnatter et al. (12) study indicates an SMR of 263 for melanoma, which was of borderline statistical significance. Several measures of increasing exposure were not related to an increase in disease risk in the latter study. However, the number of expected deaths in each category was small. The recently updated Rushton study (13) did not present analyses for malignant melanoma. It is noteworthy that the study of

Dow chemical workers exposed to benzene (30) demonstrates a significantly elevated risk of death from skin cancer. Three of the four deaths from skin cancer in the latter study were from malignant melanoma. Residence in petroleum manufacturing counties has been associated with a significantly elevated risk of death from both malignant melanoma and nonmelanotic skin cancer in comparison to residence in counties comparable by geographic region, population size, and other demographic indicators (18). In addition, the National Toxicology Program (NTP) cancer bioassay demonstrated a significant increase in tumors of the skin in male rats exposed to benzene through oral gavage (11).

## Conclusion

There is an association between malignant melanoma and employment in refineries. Whether this elevated risk is due to chemical exposure, sunlight exposure, or a combination of the two should be the subject of further evaluation. The fact that the workers spend considerable time outdoors argues in favor of the sunlight hypothesis. The Dow study results (30), the NTP bioassay results (11), and the residence in petroleum manufacturing counties results (18) argue in favor of a chemical involvement in the skin cancer.

## Heart Disease

In the Schnatter study (12), the SMR for myocardial infarction was 97, while the SMR for aortic aneurysms was 179. The highest risk was observed in those nonexposed to total hydrocarbons (SMR = 280). The tank truck drivers (highest exposure) did not have an excess of death from heart disease, though the numbers are small (1 observed versus 1.5 expected). In the Rushton study (13), there was only a slight elevation above background for heart diseases among refinery workers when the general population was used for comparison.

## Conclusion

The data currently available do not support an association between heart disease and exposure to gasoline vapor. However, analyses for causes of death (such as heart disease or lung cancer) that are associated with cigarette smoking need to control for this variable, particularly in light of comments that these workers smoke less than the general population.

## Challenge to the American Petroleum Institute on Misuse of Gasoline and Subsequent Disease

Finally, I would like to challenge the American Petroleum Institute (API) to develop a program to prevent the "misuse" of gasoline by workers and by the public in general. In September of 1990, I published in *The Lancet* an estimated relative risk of leukemia among District of Columbia municipal garage mechanics ranging from 60 to

300 based on three cases (6). These individuals had frequently siphoned gasoline by mouth. They also cleaned engine parts by soaking them in a mixture of gasoline and oil. In the article, I also mentioned two additional local garage mechanics who were recently diagnosed with leukemia as well as a roofer who was diagnosed with aplastic anemia. The latter individual used gasoline to clean seams before cementing strips of rubberized roofing material. Other people recently have informed me that they have used gasoline (taken from their gasoline can for their power lawn mower) to clean their garage floor and hands when they work on their cars at home.

In addition, recent studies of U.S. highway maintenance workers demonstrate an excess risk of leukemia (31) and lymphopoietic cancer (32). Bender et al., who conducted the Minnesota Department of Transportation study (32), are in the process of updating their cohort and have identified an additional six cases of leukemia for those with 30–39 years of work experience. In the initial report, seven deaths were observed versus 1.6 expected (SMR = 425) for this group. Bender et al. recently interviewed the highway workers and were told that the workers used gasoline to clean asphalt and other materials from their hands (personal communication). The investigators are of the opinion that the misuse of gasoline as a solvent was the most likely explanation for the excess leukemia risk observed in their study (A.P. Bender and D.L. Parker, personnel communication).

In response to my letter to *The Lancet* (6), Fleming (9) published a letter presenting analyses of peripheral blood counts among: adolescent boys and young men in Nigeria who inhale and swallow petrol while siphoning as "unofficial vendors" of petrol and heavy oil, motor mechanics employed in small workshops who use petrol as a solvent, official petrol pump attendants, and controls who were not exposed professionally to petroleum. Fleming reported statistically significant and high rates of anemia, microcytosis, thrombocytopenia, and neutropenia among the unofficial vendors and motor mechanics but not among the official vendors (9). Thus, the hazards to the blood-forming organs from the misuse of gasoline are not confined to people of the industrialized countries. Moreover, conversations with health professionals from the lesser developed countries suggest that work practices with gasoline are much worse there as compared to the United States.

The situations mentioned above indicate the disparity between knowledge of hazards among the scientific community and education of workers and the public about those hazards. In an attempt to deal with this problem, I recommend that the API and its member companies voluntarily develop a program to label gas pumps as done in Sweden. The Swedish warning states that gasoline is poisonous if inhaled; if handled in confined spaces, it can cause cancer; with normal tank filling, the health risk is small; it is dangerous to drink; and skin contact should be avoided. Or, some other language should be adopted that appropriately conveys the cancer and blood disease hazards if tank filling is not done correctly. This warning would presumably result in a reduction in the misuse of gasoline by garage mechanics, other workers, and con-

sumers in general, and at the same time allay fear and apprehension about appropriate filling procedures.

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